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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,063	02/11/2004	John S. Benco	1657/2052	2112

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EXAMINER	
SODERQUIST, ARLEN	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/776,063	BENCO ET AL.
	Examiner	Art Unit
	Arlen Soderquist	1743

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *11 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

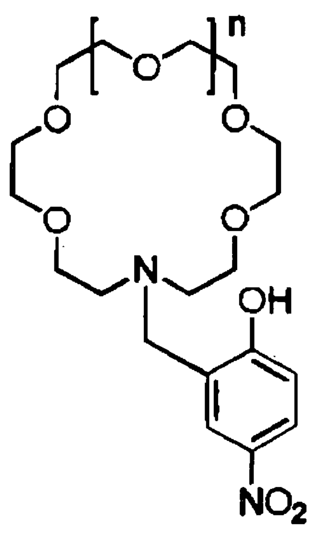
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benco (*Journal of Photochemistry and Photobiology A,* 2002) or Kim (J. Org Chem. Newly cited and applied) in view of Pacey (US 4,659,815) and Barnard (US 6,417,005 or WO 97/39337).

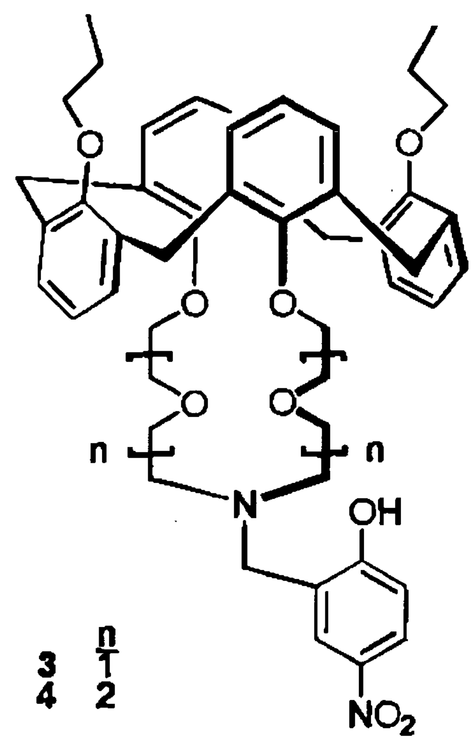
In the paper Benco teaches 9-anthryl-substituted azacrown ether covalently linked to a 1,3-alternate calix[4]arene as a fluoroionophore for the detection of potassium ions. *N*-(9-methyl-anthracene)-25,27-bis(1-propyloxy)calix[4]arene azacrown-5 (**II**) and its model compound *N*-(9-anthrylmethyl)aza-18-crown-6 (**I**) were synthesized and tested as fluoroionophores for the selective detection of potassium ions with a view to the use of **II** in the fabrication of potassium ion sensors. Compound **II** consists of a 1,3-alternate calix[4]arene group covalently linked to an azacrown ether that is *N*-substituted with a fluorescent anthracene group. This compound acts as an 'off–on' fluorescent indicator for ion complexation. In dichloromethane solution, compound **II** exhibits good sensitivity to potassium ions and forms a 1:1 fluoroionophore–ion complex. Studies demonstrate that **II** is selective for potassium over other alkali metal cations, with excellent selectivity over sodium and lithium (log $K_{K,Na}$~log $K_{K,Li} \leq$-3.5) and moderate selectivity over rubidium and cesium (log $K_{K,Rb}$~log $K_{K,Cs}$~−1). Sensitivity of **II** to potassium is considerably enhanced in dichloromethane in comparison to methanol/dichloromethane mixtures, presumably due to two effects: a hydrogen-bonding interaction of methanol with the azacrown nitrogen atom, and poor solvation of the ion by

dichloromethane, the latter creating a driving force for complexation. On page 37 there is a discussion of selectivity. The first sentence of this section teaches that the eventual intention is to use molecules similar to II as a sensor. The next sentence teaches that given the structural similarities between II and 1,3 alternate calix[4]arenas, it is reasonable to expect similar binding properties. The next sentence teaches that they expect metal complexation in II to be governed by electrostatic interactions (primarily cation-π interactions). That sentence also teaches that the selectivity is primarily controlled by a size fit effect and steric effects from the propyl substituents appended to the two rotated aryl rings of the calix[4]arene. Benco does not teach an azacrown calix[4]arene sized to capture lithium or structures related to sensor formation.

In the paper Kim teaches the synthesis and metal ion complexation studies of proton-ionizable calix[4]azacrown ethers in the 1,3-alternate conformation. A series of novel N-chromogenic calix[4]arene azacrown ethers shown below as compounds 3-4 were synthesized. The azacrown compounds 1-2 were also synthesized and the metal complexation/extraction behavior was measured. Page 2386 discusses the known use of both of these types of structures for determination of metal ions. Structure 1 was found to have lithium selectivity while



	n
1	0
2	1



	n
3	1
4	2

compound 2 showed potassium selectivity due to size agreement between the metal ion and the cavity of the corresponding azacrown ether. The paragraph bridging pages 2386-2387 discusses calixcrown ethers as 3-D molecular building blocks for receptors of metal cations. For cesium in particular, a calixarene crown derivative is exceptionally good due to the complexation of cesium ion not only with the crown ether but also with the two aromatic rings (cation/π-interaction) when fixed in the 1,3-alternate conformation . The first full paragraph of page 2387 teaches that based in this, **it is possible that the combination of *N*-chromogenic azacrown ether and calixcrown ether would result in an optimized structure for metal ion encapsulation** due to (1) electrostatic interactions between the metal ion and both the oxygens and a nitrogen as electron donors, (2) π-metal interactions between the metal ion and two rotated aromatic nuclei of the 1,3-alternate calixarene, and (3) an extra pendant chromogenic group attached to nitrogen, which can promote metal complexation by 3-D encapsulation under basic conditions. With this in mind, they sought to synthesize chromogenic calixazacrown ethers and to investigate their complexation behavior **toward alkali metal ions** through bulk liquid membrane, solvent extraction, and ^{1}H NMR studies. The chromogenic calix[4]arene azacrown ethers were prepared in moderate yields by reacting dipropyloxybis(chlorooxapentyl)calix[4]arenes with p-toluenesulfonamide in the presence of potassium carbonate; reductive removal of the tosyl group and alkylation of the amine with 2-hydroxy-5-nitrobenzyl bromide. Tables 1-3 show the results of the tests with high transport selectivity for potassium over other metal ions for compound 3 as shown by two-phase extraction, bulk liquid membrane, and 1H NMR studies on a ligand-metal complex. It is assumed that the OH of the chromogenic group attached on nitrogen can assist the complexation by encapsulation of the metal. Compound 3-4 are based on the structure of compounds 1-2. Kim does not teach an azacrown calix[4]arene sized to capture lithium or structures related to sensor formation.

In the patent Pacey teaches chromogenic aza-12-crown-4 ethers used for the spectrophotometric determination of lithium ion in aqueous solutions. The compounds are particularly useful for the analysis of lithium in the presence of Na^{+}, a situation common in biological and geological systems. The compounds [e.g., 1-(2-oxy-5-nitrobenzyl)-1-hydro-1-aza-4,7,10-trioxacylclododecane] are similar in structure to compound I of Benco except they have a smaller crown and a colorimetric group appended to the crown. Column 1, lines 30-43

teach that selective reagents permitting the isolation of a particular ion from a complex matrix or mixture of ions are of interest to those in the chemical or bio-chemical analytical fields. When the matrix in question includes two or more cations of the Group I metals, it is often difficult to selectively isolate one of the Group I cations from the mixture without interference from other cations in the system. With respect to biological systems, such as blood serum, which contains a relatively large amount of sodium ion, a reagent having the ability to selectively (and quantitatively) extract lithium ion in the presence of sodium ion is of interest for bio-chemical assays. Some examples of prior art molecules are taught with drawbacks being explained. Column 3, lines 11-19 and example 9 teach the selectivity of the molecules of the invention when lithium is complexed in the presence of a large excess of sodium. Example 7 shows the ability of the reagents to complex lithium in the presence of a potassium hydroxide buffer and example 11 shows the ability to measure lithium in blood and urine samples. These results shown in table 2 show excellent correlation with the known amount of lithium present.

In the patent and published application Barnard teaches covalently immobilized fluoroionophores as optical metal ion sensors. Since both are members of the same patent family only the US patent will be described but corresponding disclosure also exists in the published application. Fluoroionophores that are fictionalized with reactive groups may be covalently bound to inorganic or organic carrier materials and are used as active components in polymer membranes of optical sensors for the detection of ions. The sensors are distinguished by a long usable life and a high degree of sensitivity. In the formula taught, and ionophore, I, can have a number of forms and are natural or synthetic organic compounds that contain a plurality of mostly alternating electron-rich hetero atoms such as, for example, S, N and especially O, in an open-chained or cyclic carbon chain and that enable the ions to be measured to be selectively complexed. Column 2, line 60 to column 3, line 7 teach these ionophores derived from substances that have an oligoether, polyether, oligoester, polyester, oligoamide or polyamide structure. Examples of such suitable substances may be crown ethers, coronandenes, cryptandenes, **calixarenes**, podandene or derivatives thereof, also cyclic peptides, for example valinomycin, nonactin, peptides such as gramicidin, and peptides which in the presence of the ion to be determined change their secondary, tertiary or quaternary structure for bonding the ion; it is also possible to use tetrahydrofuran-containing macrolides bonded via ester bridges, and

analogous substances that are able to regulate transport in biological systems, or cyclic oligosaccharides, such as, for example, cyclodextrins or cyclophanes. Columns 5-8 show the structure of several of these with structure (IV) being a calix[4]arene. Columns 8-11 show various examples of the fluorophores used in the fluoroionophores. Columns 13-18 specifically show structures of three calix[4]arene fluoroionophores. Columns 20-22 teach a wide variety of carrier materials. Column 29 teaches that the compositions taught may be applied to suitable support materials. The support is preferably transparent and may be formed, for example, from a plastics material, such as, for example, polycarbonate or acrylic glass, mineral materials, metal oxides or glass, and may be of any shape, for example in the form of plates, cylinders, tubes, strips or fibers. The optical range in which the material as sensor can be excited extends from the ultraviolet range to the infrared range. The immobilized fluorophore-ionophores have very suitable absorption and emission wavelength ranges that allow the use of known economically priced low-energy light sources, for example halogen or xenon lamps or light-emitting diodes. Commercially obtainable optical fibers may be used in the excitation and detection. Column 30 teaches that one very important advantage is that the immobilized fluoroionophores can carry out the analyses being substantially independent of pH and therefore may be carried out directly in body fluids such as blood, urine and serum. Among the many cations that the compounds can be used for, the alkali metal ions including lithium are preferred cations (column 30).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the azacrown portion of the Benco or Kim fluoroionophore to correspond to that of the difference between the model azacrown of Benco or Kim and the similar azacrown of Pacey because of the recognition by Benco or Kim that the binding is related to the size fit and other types of effects and the teaching in Pacey that lithium is an important analyte that can be complexed by the smaller azacrown with a high selectivity with respect to the complexation of sodium and other alkali metals in a biological sample. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the fluoroionophore of Benco into a carrier material and or onto a support as taught by Barnard because of the advantages in carrying out the analysis as taught by Barnard.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 in view of Benco, Pacey and Barnard as explained above. The patented claims are directed to a molecule, device and method that encompass the molecule, device and method taught by Benco above, therefore they differ from the instant claims as the Benco reference differs from the instant claims. Thus for the reasons given above, the instant claims are obvious in view of the patented claims.

5. Applicant's arguments filed November 18, 2004 have been fully considered but they are not persuasive. Relative to the rejections, examiner points to the fact that both the Benco and Kim papers developed. the calixarene azacrowns based on the structure of azacrown ethers. Both tested the complexation abilities with a series of alkali metals (see the figures and tables of both papers. Both series included lithium, sodium and potassium. Thus the tests performed were looking to see the complexation abilities of the compounds with all of the metals and found that the complexation with potassium was the strongest for compound 3 of Kim and compound II of Benco. Both Benco and Kim recognize that one reason involved in the complexation behavior is the size of the cavity. The Pacey reference teaches two important things: the measurement of lithium in biological fluids is important and an azacrown having a smaller cavity than the model compounds of Benco and Kim complexes well with lithium. Thus one of skill in the art would have expected that the calixarene azacrown ethers of Kim and Benco with smaller azacrown portions consistent with the size difference between the ring size of the Kim and Benco model compounds and the Pacey compound would have selectivity towards lithium based on at least the size aspect. Also the person of skill in the art would have done it due to the desire to measure

lithium as taught by Pacey and the potential for a 3-D encapsulation providing an optimized structure as taught by Kim. These same reasons apply to the obviousness-type double patenting rejection. Kim is clearly not directed to a potassium ion sensor as its sole purpose and Benco as well was not directed to a potassium ion sensor. Examiner states that if the complexation behavior of the Benco and Kim compounds were different, the papers would have reported the different results. Thus that papers are reporting the results and the focus of the papers is based on the results. As an example of this, applicant is directed to the results of compound 4 of Kim which are different from compound 3. The Kim paper presents the results of both compounds and discusses them also, even though they are different. In the same way the Benco paper is reporting the results of the tests Benco conducted. The fact that potassium is a metal that there is a desire to measure simply enhances that value of the results and allows Benco to focus the discussion in that direction. Kim on the other hand is more generally focused and shows more of the scope of understanding by those of the art. Therefore, since there is a desire to find compounds for measuring lithium as shown by Pacey, there is motivation to make the suggested change based on the difference in ring size between the azacrown ethers of Benco or Kim and Pacey. For these reasons the Barnard reference does not need to modify the compounds of Kim or Benco in that manner. It does clearly teach benefits of placing compounds intended to measure metal ions in various formats. That is how it has been used.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art is directed toward molecules and methods for complexing metal ions with azacrown ethers and calixarenes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Arlen Soderquist

December 30, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER